REMARKS

Claims 1, 2, 6-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33, 46-49 and 102 are currently pending in the present application. Claims 46-49 have been withdrawn by the Examiner as drawn to a non-elected species. Applicants reserve the right to rejoin these claims when a generic claim is allowed. Claim 2 is amended herein. Support for this amendment may be found in the specification at least at page 5, line 26-28. After entry of the present Amendment, claims 1, 2, 6-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 102 will be pending.

I. The Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement, Should Be Withdrawn

Claim 11 remains rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled. While the Examiner acknowledges that the specification is enabling for methods of modulating certain aspects of proliferation and differentiation of mammalian stem or progenitor cells with certain PDE IV inhibitors, the Examiner contends that the specification is not enabling for methods of inducing specific differentiation end points, in particular differentiation of a stem cell into a cell that expresses a particular combination of differentiation markers. Office Action at page 5. This rejection is traversed. Reconsideration is respectfully requested.

It is respectfully submitted that the scope of claim 11 has been misinterpreted by the Examiner. It seems that the Examiner is under opinion that Claim 11 is drawn to a method of modulating the differentiation of $CD34^+CD38^-CD33^-$ cells into $CD34^+CD38^-CD33^+$ cells (Office Action, page 5) by contacting with a PDE IV inhibitor of a specific structure. In fact, the scope of claim 11 covers a method of modulating of differentiation of a hematopoietic stem cell or hematopoietic progenitor cell (for example, $CD34^+$ cell) into a $CD34^+CD38^-CD33^-$ cell or a $CD34^+CD38^-CD33^+$ cell.

The instant specification teaches that $CD34^+$ and $CD133^+$ are early progenitor cells. These cells can be induced under certain circumstances (for example, by contacting with a PDE IV inhibitor of a certain structure) to differentiate into specific cell lineages such as myeloid or granylocitic lineages (for $CD34^+$ cells) or endothelial or neural cell lineages (for $CD133^+$ cells) (*see*, for example, page 19, lines 19-31 of the instant specification). Thus, it would be expected that a hematopoietic stem cell or hematopoietic progenitor cell would differentiate into, *e.g.*, macrophages and/or monocytes, well-known CD33 marker carriers. Additionally, modulation of differentiation of $CD34^+$ progenitor cells is described in

Example 11. The Example teaches that $CD34^+$ progenitor cells are induced by the compounds of the invention to acquire the CD33 myeloid marker.

Therefore, it is respectfully submitted that the instant specification provides sufficient guidance for treating of $CD34^+$ progenitor cells with a specific PDE IV inhibitor to yield a cell that expresses the myeloid marker (CD33), as claimed in claim 11. Thus, the specification enables a person skilled in the art to make and to use the invention commensurate in scope with claim 11. Accordingly, it is respectfully requested that the rejection of claim 11 under 35 U.S.C. § 112, first paragraph, be withdrawn.

II. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for not further limiting the subject matter of claim 1. Reconsideration is respectfully requested in view of the amendments made to claim 2.

Applicants have amended claim 2 to recite a method for modulating the differentiation of a hematopoietic stem or progenitor cell into a blood cell. It is believed that as amended claim 2 is sufficiently clear. Therefore, it is respectfully requested that the rejection of claim 2 under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. The Rejection Under 35 U.S.C. 103(a) Over Elsas in view of Muller and Janowska

Claims 1, 2, 7-9, 16, 25, 26, 29, 30, 32, 33 and 102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gaspar Elsas *et al. (British Journal of Pharmacology* 130: 1362-1368, 2000, hereinafter, "Elsas") in view of Muller (U.S. Patent 6,020,358, hereinafter, "the '358 patent") and Janowska-Wieczorek *et al.* (*Blood* 98:3143-3149, 2001, hereinafter, "Janowska"). In particular, the Examiner is of the opinion that a person of ordinary skill in the art would have had a reasonable expectation of success in substituting the compound used by Muller into the method of Elsas, as the compounds used by Muller and Elsas are PDE IV inhibitors. This rejection is traversed. Reconsideration is respectfully requested.

It is a well-established legal principle that a finding of obviousness requires that the prior art both suggests the invention and provides one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). In the instant case, the art cited by the Examiner neither suggests the invention as claimed nor provides a skilled artisan with a reasonable expectation of success, as explained below.

The instant claims are drawn to a method for modulating the proliferation or differentiation of a mammalian hematopoietic stem cell or hematopoietic progenitor cell by contacting with an PDE IV inhibitor of a specific structure. Elsas allegedly teaches that different compounds including rolipram (a PDE IV inhibitor) are capable of modulating a degree of colony formation by hematopoietic stem cells of mouse bone marrow. Elsas does not teach contacting hematopoietic stem cells or hematopoietic progenitor cells with a compound of structure VII, as claimed (as admitted by the Examiner, Office Action, page 8). Additionally, the Examiner alleges that different PDE IV inhibitors are substitutable regardless of their structure, which is not accurate. This is neither taught nor suggested by Elsas or the pertinent art. As such, the reference does not teach or suggest a method for modulating a differentiation of a hematopoietic cell or a hematopoietic progenitor cell, as instantly claimed.

Contrary to the Examiner's allegations that Muller remedies the deficiencies of Elsas, it does not. Muller does not teach a method for modulation of differentiation of stem cells using the disclosed compounds. Neither he provides a suggestion or motivation to modify the teachings of Elsas to arrive at the invention as claimed as Muller teaches a different utility of the disclosed compounds. Therefore, it is respectfully submitted that a skilled artisan would not have a reasonable expectation of success by using the compound taught by Muller with respect to the method of Elsas. Therefore, such combination does not render the instant method obvious.

Janowska purportedly discloses $CD34^+$ cells encompassing platelet-binding ligands. The reference is silent as to contacting the cells with a PDE IV inhibitor (as admitted by the Examiner, Office Action, page 10). As such, the combined purported teachings of Elsas, Muller and Janowska do not provide a reasonable expectation of success in arriving at the invention as claimed and, therefore, do not render the claimed method for modulating a differentiation of hematopoietic stem or progenitor cells obvious over the cited art. Accordingly, it is respectfully requested that the rejection be withdrawn.

IV. The Rejection Under 35 U.S.C. 103(a) over Elsas in view of Muller, Janowska and Waki

Claims 1, 2, 7-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Elsas in view of Muller and Janowska, in further view of Waki *et al.* (*Japan Journal of Pharmacology* 79:477-483, 1999, hereinafter, "Waki"). In particular, the Examiner is of the opinion that a person of ordinary

skill in the art would have had a reasonable expectation of success in substituting the compound used by Muller for the compound used by Waki because the two are functional equivalents. This rejection is traversed. Reconsideration is respectfully requested.

In traversing the rejection, Applicants apply the same legal standard as used in section III above and respectfully submit that the combined teachings of Elsas, Muller, Janowska and Waki do not provide a skilled artisan with a reasonable expectation of success, as explained below.

Waki purportedly teaches the use of 1-*n*-butyl-3-*n*-propylxanthine in osteopenia. Although a PDE-IV inhibitor, the disclosed compound is used for a different purpose and is structurally distinct from the compound of the claimed invention. As addressed in section III above, various PDE-IV inhibitors are not substitutable. Therefore, the disclosure of Waki does not suggest or motivate to modify the teachings of Elsas or Muller to arrive at the claimed invention. Neither do the combined alleged teachings of Elsas, Muller, Janowska and Waki, as explained in the arguments presented in section III above, to which we hereby refer. Accordingly, it is respectfully requested that the rejection be withdrawn.

V. The Rejection Under 35 U.S.C. 103(a) over Waki in view of Muller and Janowska

Claims 1, 2, 7-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Waki in view of Muller and Janowska. In particular, the Examiner is of the opinion that a person of ordinary skill in the art would have had a reasonable expectation of success in substituting the compound used by Muller into the method of Waki because the two compounds are PDE IV inhibitors. This rejection is traversed. Reconsideration is respectfully requested.

In traversing the rejection, Applicants again apply the same legal standard as used in section III above and respectfully submit that the combined teachings of Waki, Muller and Janowska do not provide a skilled artisan with a reasonable expectation of success.

As discussed in section IV above, Waki purportedly teaches the use of a new PDE IV inhibitor, 1-*n*-butyl-3-*n*-propylxanthine (XT-44), for treating osteopenia, including osteoporosis. The author apparently suggests the oral administration of the compound to an animal and *in vitro* contact of the rat bone marrow cells with XT-44. The compound taught by Waki is structurally distinct from the compound of the instant invention. Therefore, Waki does not teach or suggest the claimed method as treating of osteopenia and osteoporosis are not the goals of the instant invention but rather the modulation of differentiation of hematopoietic stem and progenitor cells.

The alleged combined teachings of Muller and Janowska do not remedy the deficiencies of Waki, as explained in the arguments presented above in the instant response.

Therefore, based on aforementioned, it is respectfully submitted that the claimed method for modulating a differentiation of haemopoietic stem or progenitor cells by a PDE IV inhibitor of the formula of claim 1 is not obvious over the cited art. Accordingly, it is respectfully requested that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the present remarks be made of record in the file history of the present application. An early allowance of the application is earnestly requested. The Examiner is invited to contact the undersigned with any questions concerning the application.

No fee, other than an extension of time fee, is believed to be due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. § 1.17 or credit any overpayment, to Jones Day U.S. Deposit Account No. 503013, referencing Attorney Docket No. 9516-149-999 (CAM:501872-999148).

Respectfully submitted,

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